Adverse Events Related to Therapy

KAPOSI SARCOMA IN AN IMMUNOSUPPRESSED PATIENT WITH PRESUMED CROHN'S DISEASE: IATROGENIC OR EPIDEMIC?

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Introduction: Biologic immunosuppression and HIV infection both carry risks of infection and malignancy. Small series suggest that patients living with well-controlled HIV may safely and efficaciously use biologics, like TNF-alpha inhibitors (TNF-I). However, no current U.S. guidelines exist to screen for HIV infection among high-risk groups prior to starting TNF-I. We describe the case of a patient who received TNF-I for Crohn's Disease without any HIV testing, who developed potentially avoidable extensive Kaposi Sarcoma.

Case Description: A healthy 32-year-old man presented with 1 month of diarrhea and a 15-lb weight loss. Fecal calprotectin, ESR, and CRP were markedly elevated. Endoscopy demonstrated severe rectal inflammation with perirectal abscess and perianal skin tags, suggestive of inflammatory bowel disease. Biopsies showed active colitis with ulceration, cryptitis, and fibropurulent debris without evidence of granulomata, dysplasia, or CMV. He was treated with IV antibiotics, IV steroids, and 2 infusions of infliximab at 5 mg/kg. He continued to have 4 loose stools an hour, limiting his steroid wean.

One month later, he developed painful, violaceous plaques on his face, buccal mucosa, torso, and lower extremities. Biopsy showed Kaposi Sarcoma, and HIV test was positive, with viral load 3292 and CD4 count 248. Although in a monogamous relationship with his husband, a well-recognized risk factor for HIV acquisition, he had never been tested for HIV. Antiretroviral therapy was initiated promptly.

Repeat rectal biopsies stained positive for HHV-8 and CMV, concerning for rectal KS and CMV proctitis. He started valgancyclovir but self-increased prednisone, with poor symptom relief. Review of the initial endoscopy confirmed no obvious HHV-8 positivity. Three weeks after HIV diagnosis, he developed new red nodules across his chest, suspicious for worsening KS due to immune reconstitution inflammatory syndrome (IRIS). He completed 12 cycles of chemotherapy and had no sign of residual IBD on recent colonoscopy. KS is his presumed original diagnosis.

Discussion: Current U.S. guidelines do not recommend HIV screening prior to TNF-I use, despite the heightened risks of cumulative immune dysregulation. Our patient should have been screened annually for HIV according to CDC guidelines. Further, his uncontrolled HIV infection in combination with TNF-I and high dose steroids led to life-threatening Stage IV malignancy (KS), complicated by immune reconstitution inflammatory syndrome and poor ART absorption. We propose that all patients should be screened for common risk factors for HIV acquisition, such as men who have sex with men or intravenous drug use. For high risk patients, gastroenterologists should consider screening for HIV, in addition to tuberculosis and hepatitis, prior to immunosuppression with TNF-I.

SAFETY OF AMISELIMOD IN HEALTHY SUBJECTS: RESULTS FROM A PHASE 1 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Objective: To evaluate the safety profile of amiselimod, a selective sphingosine 1-phosphate receptor modulator which has been shown to regulate lymphocyte trafficking and is in development for the treatment of inflammatory bowel disease.

Methods: A randomized, double-blind, multiple-dose, placebo-controlled, parallel study with a nested crossover design evaluated the safety and tolerability profile of amiselimod. Healthy adults were randomized in a 2:1:1 ratio during a 28-day treatment period accordingly: a single dose of placebo followed by oral amiselimod (upwardly titrated in doses ranging from 0.4 to 1.6 mg to achieve 0.4 mg and 0.8 mg steady-state exposure; a single dose of oral moxifloxacin 400 mg followed by placebo; or placebo followed by a single dose of moxifloxacin 400 mg. The safety population included all subjects who received at least one dose of treatment. Adverse events (AE) and serious AEs were collected. Treatment-emergent AEs were defined as an AE that was starting or worsening at the time of or after study drug administration. Changes in clinical laboratory parameters (including lymphocyte counts), physical examinations, vital signs, and electrocardiogram parameters (including heart rate, PR, QRS, and QT intervals) were recorded. Subjects were permitted to withdraw if lymphocyte counts were ≤ 0.2 x 10^9/L.

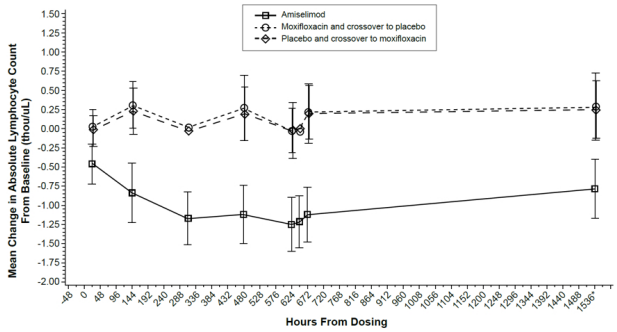
Results: The safety population included 190 subjects of which 95 received amiselimod and 95 were in the combined moxifloxacin group. Subjects were 40% female, 83% white, and the mean (standard deviation) age was 39.0 (8.8) years. The discontinuation rate was 8% (n=8) in the amiselimod group and 4% (n=4) in the moxifloxacin group. Three subjects who received amiselimod discontinued because they met the stopping criteria for low lymphocyte counts. One subject experienced an amiselimod-related serious AE of atrial fibrillation on day 26 (after receiving amiselimod 1.6 mg for 3 of the preceding 4 days) that required hospitalization, cardioversion, and led to discontinuation. No deaths were reported. All other AEs were mild to moderate in severity. Decreased white blood counts were the most commonly reported TEAE, followed by headache and constipation (Table). Reductions in white blood counts returned to normal range after study discontinuation without sequelae. Decreased neutrophils, lymphocytes and hemoglobin, and increased creatine kinase, alanine aminotransferase, and aspartate aminotransferase were reported, all of which resolved without sequelae. The mean absolute lymphocyte count for amiselimod exhibited a gradual decrease from predose (1.681 thou/uL) to a nadir of 0.424 thou/uL on day 27 (Figure). Changes to vital signs, physical examinations, and ECG parameters were within normal limits.

Conclusions: Upwardly titrated doses of amiselimod ranging from 0.4 to 1.6 mg were generally well tolerated in healthy subjects.

Table. Treatment-Emergent Adverse Events (>5%) by Treatment Group–Number of Subjects Reporting an Event (% of Subjects Dosed)

Adverse Event, n (%)	Amiselimod (Days 1–13 up to 0.4 mg steady state exposure) n=95	Amiselimod (Days 14+ up to 0.8 mg steady state exposure) n=92	Moxifloxacin (Days 1–27+) n=93	Placebo (Days 1-26) n=48
Number of subjects with an adverse event	55 (58)	57 (62)	30 (32)	26 (54)
White blood cell count decreased	18 (19)	13 (14)	0	0
Constipation	8 (8)	6 (7)	5 (5)	6 (13)
Dizziness	5 (5)	6 (7)	2 (2)	0
Headache	4 (4)	11 (12)	7 (8)	5 (10)
Upper respiratory tract infection	1 (1)	6 (7)	1 (1)	0

Figure. Arithmetic Mean (Standard Deviation) Change in Absolute Lymphocyte Counts from Baseline (thou/uL) vs Time for Treatment



THE CUMULATIVE INCIDENCE OF POUCHITIS AND POUCH-RELATED COMPLICATIONS IN PEDIATRIC PATIENTS WITH ULCERATIVE COLITIS

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Background & Aims: Despite highly effective therapies, many children develop medically refractory ulcerative colitis (UC) and undergo proctocolectomy with ileal pouch anal anastomosis (IPAA). There is little real world evidence regarding IPAA outcomes in pediatric UC patients. We sought to determine the risk of pouchitis, recurrent pouchitis, and change in diagnosis to Crohn's disease (CD) within two years of IPAA surgery among pediatric patients with UC using a large, geographically diverse insurance claims database.

Methods: Within the IQVIA Legacy PharMetrics Adjudicated Claims Database, we identified pediatric patients (age <18 years) with UC who underwent proctocolectomy with IPAA between January 1, 2007 and June 30, 2015. We utilized International Classification of Diseases (ICD-9-CM or ICD-10-CM) codes to identify

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patients with UC and Current Procedural Terminology III codes to identify IPAA. The primary outcome was the development of pouchitis in the first 2 years following surgery, as identified by a previously validated case-finding definition. Secondary outcomes included the incidence of recurrent pouchitis, and the cumulative incidence of a new diagnosis of Crohn's disease (CD) in the first two years post-IPAA. A change in diagnosis to CD was identified by an ICD-9-CM or ICD-10-CM code for CD on at least three separate occasions. Bivariate analyses were used for all comparisons, utilizing chi-square and t-test as appropriate.

Results: A total of 68 patients with an IPAA with at least two years of continuous health plan enrollment following surgery were identified. Among all patients undergoing surgery, the median age was 15 years (interquartile range 11.5–16), with 29 (43%) female patients. In the first 2 years following IPAA, the cumulative incidence of pouchitis was 54%. Characteristics and prior medical treatments in patients without pouchitis and with ≥ one episode of pouchitis were similar (Table 1). The cumulative incidence of recurrent pouchitis during this period was 22%. The cumulative incidence of a new diagnosis of CD in the two years after IPAA for UC was 9%.

Conclusions: In a geographically diverse cohort from the United States, 54% of pediatric patients undergoing proctocolectomy with IPAA for UC developed pouchitis within the first two years after surgery. Furthermore, 9% had a change in diagnosis to CD. These data indicate that for many pediatric UC patients, surgery is non-curative and patients continue to have a substantial burden of illness. Future efforts should attempt to identify novel, actionable, predictors of pouchitis in this population.

Table 1. Demographic and clinical characteristics of patients with and without pouchitis in the two years following an ileal pouch-anal anastomosis

	Patients without pouchitis (n=31)		Patients with pouchitis (n=37)		p-value
	n	%	n	%	
Age in years (Mean, SD)	12.2	4.2	13.9	3.3	0.058
Female Sex	11	35	18	49	0.274
***Clostridioides difficile* infection in 6 months prior to colectomy with IPAA**	1	3	1	3	0.899
Primary Sclerosing Cholangitis	0	0	3	8	0.105
Diagnosis of colon cancer or dysplasia in 6 months prior to colectomy with IPAA	4	13	1	3	0.108
Residence Region					0.317
Northeast	7	23	4	11	
Midwest	11	35	21	57	
South	7	23	7	19	
West	6	19	5	14	
Pay type					0.329
Commercial Plan	18	58	27	73	
Medicaid	8	26	3	8	
Self-Insured	1	3	5	14	
Unknown/Missing	4	13	2	5	
Year of index date					0.217
2007	2	6	0	0	
2008	5	16	3	8	
2009	3	10	8	22	
2010	5	16	10	27	
2011	6	19	7	19	
2012	3	10	1	3	
2013	1	3	5	14	
2014	2	6	1	3	
Therapy in the 6 months prior to colectomy					
Mesalamine	12	39	17	46	0.548
Sulfasalazine	3	10	3	8	0.820
Immunomodulator (thiopurine or methotrexate)	13	42	19	51	0.438
Anti-tumor necrosis factor alpha	9	29	10	27	0.854

Ileal pouch-anal anastomosis (IPAA); standard deviation (SD)

Animal Models: Pre-Clinical Treatment of Intestinal Inflammation

ADVANCING HIGH TECH DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF CROHN'S DISEASE

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Introduction: High tech drug delivery systems, which allow for precise location targeting and efficient delivery mechanisms, can reduce the risk of side effects and increase dosage effectiveness in the treatment of Crohn's disease. We describe a revolutionary capsule technology which uses radiofrequency signaling to trigger an optimal release of the pharmaceutical contents to specified regions of the gastrointestinal tract.

System and method: Data were observed in two groups of female Yorkshire-Cross swine. Intra-cecal ports were surgically placed in Group 2 swine. After baseline analysis was complete, all study animals were administered the SmartTab capsule (Group 1 administration via balling device, Group 2 administration via intra-cecal port) containing caffeine, barium sulfate, citric acid, and sodium bicarbonate. SmartTab capsules were activated by a radiofrequency triggering event, immediately following administration in Group 2 swine and 30 minutes following administration in Group 1 swine. Blood samples were taken at 0.25, 0.50, 1, 2, 3, and 6 hours after dosing and capsule activation was confirmed using a C-Scan.

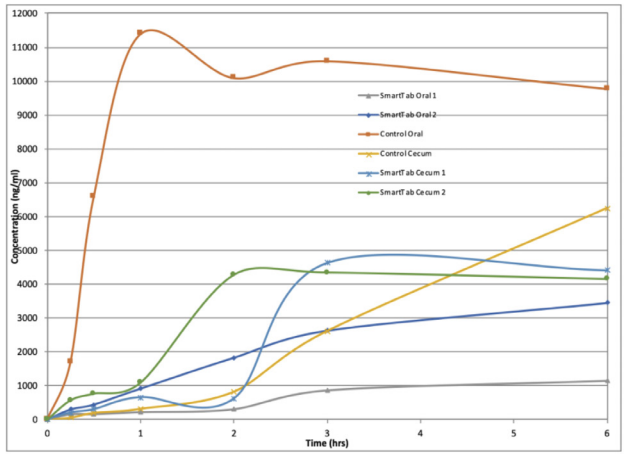
Results: Pharmacokinetic analysis revealed increased caffeine concentrations in the targeted areas. Absorption was significantly higher and more consistent in the cecum targeted administration of the SmartTab compared to the control. Although, caffeine concentrations in the stomach regions were fairly similar amongst both the experimental and control groups.

Conclusions: Via radiofrequency signaling, the SmartTab capsule can successfully administer active ingredients to the target site. With pre-installed onboard sensors, enabling the devices to send real-time data to physicians and personalize treatments using AI algorithms, this technique holds the potential to generate further advancement in high-tech drug delivery systems. Preparations are currently in order to reapply this technology in the form of an injection capsule.

Summary of Control and SmartTab Capsules (Oral and Cecum)

Time (hrs)	Control Oral	Control Cecum	SmartTab Oral 1	SmartTab Oral 2	SmartTab Cecum 1	SmartTab Cecum 2
0	0	0	0	0	0	0
0.25	1710	59.6	161	301	202	570
0.5	6600	200	165	448	303	768
1	11400	322	224	917	659	1090
2	10100	826	312	1830	619	4270
3	10600	2620	874	2630	4640	4340
6	9780	6250	1160	3450	4420	4150

Concentration (ng/mL)



All 6 PK Curves

DIETARY FIBER GUAR GUM EXACERBATES COLONIC INFLAMMATION IN MULTIPLE EXPERIMENTAL MODELS OF INFLAMMATORY BOWEL DISEASE

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The role of fermentable dietary fibers in patients with inflammatory bowel disease (IBD) is not understood. Herein, we elucidated the effect of dietary fiber guar gum, commonly added to a wide range of processed foods, on colonic inflammation. The use of three different IBD models allowed us to examine the effect of guar gum on various aspects of human IBD, such as immune hyperactivity [IL-10 receptor (IL-10R) neutralization], epithelial injury [dextran sulfate sodium (DSS)], and infection [*Citrobacter rodentium (CR)*]-mediated inflammation.

Wild-type (WT, C57BL/6) mice fed either control cellulose (insoluble fiber, *aka* non-fermentable fiber) or guar gum (soluble fiber, *aka* fermentable fiber, 7.5% w/w) were administered four weekly injections of IL-10R neutralizing antibody (α-IL-10R) to induce immune-hyperactivation mediated chronic colitis. Guar gum treated mice developed robust α-IL-10R mediated colitis. Guar gum fed mice had splenomegaly, colomegaly, elevated systemic proinflammatory markers [serum amyloid A (SAA), lipocalin 2 (Lcn2) and keratinocyte-derived chemokine (KC)] and elevated colonic Lcn2 and interleukin (IL)-1β, and histopathology scores compared to control, cellulose-fed, mice. Similar results were observed in Toll-like receptor 5 deficient mice, which are prone to develop microbiota-dependent colitis. Next, to examine the effect of guar gum on the epithelial injury model, mice were treated with DSS (1.4% w/v in drinking water) for seven days. The guar gum fed group developed severe colitis, including reduced body weight, diarrhea, rectal bleeding, shortening of colon length, and elevated levels of pro-inflammatory markers (Lcn2, KC, and SAA)compared to the control group. The last model to be tested was infection-induced colitis. Since inflammation is required